



“Optimal surfactant delivery protocol using the bovine lipid extract surfactant: a quality improvement study”

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Abstract

Importance Episodes of severe airway obstruction (SAO) are reported during surfactant administration.

Objective To evaluate adherence to and impact of a surfactant protocol on adverse events.

Methods An evidence-based protocol for surfactant administration was developed (2011), implemented (2012) and re-implemented (2014), including three major steps: lung recruitment, manual bagging, and bolus instillation. Three epochs were evaluated: E_0 (2010), E_1 (2015) and E_2 (2018). Adherence was defined as compliance with all steps. Adverse events such as hypoxia (<80%) and severe airway obstruction (SAO) were investigated.

Results 197 infants (246 administrations) were included: E_0 81 (110), E_1 52 (63), and E_2 64 (73). Adherence improved from 49% (E_1) to 67% (E_2). Full adherence to protocol significantly decreased SAO from 26% to 1.25% (E_2 ; $p < 0.005$) and hypoxia/bradycardia events (5 to 0% E_2 ; $p < 0.005$), without any side effects.

Conclusions Adherence to a surfactant administration protocol improved over time and significantly decreased important adverse events.

Introduction

Even though surfactant has been effectively used in neonates for several decades [1–4], the best instillation technique for optimal delivery into the pulmonary airways is still unclear. This is quite noteworthy since administration technique, to assure homogenous distribution, is recognized as a major component of therapy efficacy [5–8]. In addition,

it is unknown if the technique should change based on the population being treated and drug composition and/or volume; and how this can affect distribution.

The Bovine Lipid Extract Surfactant (BLES® Biochemicals Inc., London, Canada) has 27 mg of phospholipid/mL and should be administered at a dose of 5 mL/kg (135 mg of phospholipid) [9]. This low cost surfactant has been used since 1983 but some adverse events were reported during instillation in infants with birth weight <1000 g [10]. The most stark was the occurrence of severe airway obstruction (SAO) during or immediately after delivery, which lead to significant hypoxia, hemodynamic changes, and ultimately the need of endotracheal tube (ETT) removal and reintubation. Indeed, a number of these events were observed in our unit during the administration of bovine lipid extract surfactant. The clear reason why these events occurred is unknown but in extremely preterm infants, delivery of surfactant without disconnection from the ventilator was associated with a high incidence of airway obstruction [11]. Therefore, adverse events during surfactant delivery might be related to the technique, and type of surfactant and/or targeted population.

With the increased and effective use of non-invasive respiratory support at birth, surfactant administration is now mostly used in smaller and more immature preterm infants, a population under higher risks of complication. Therefore,

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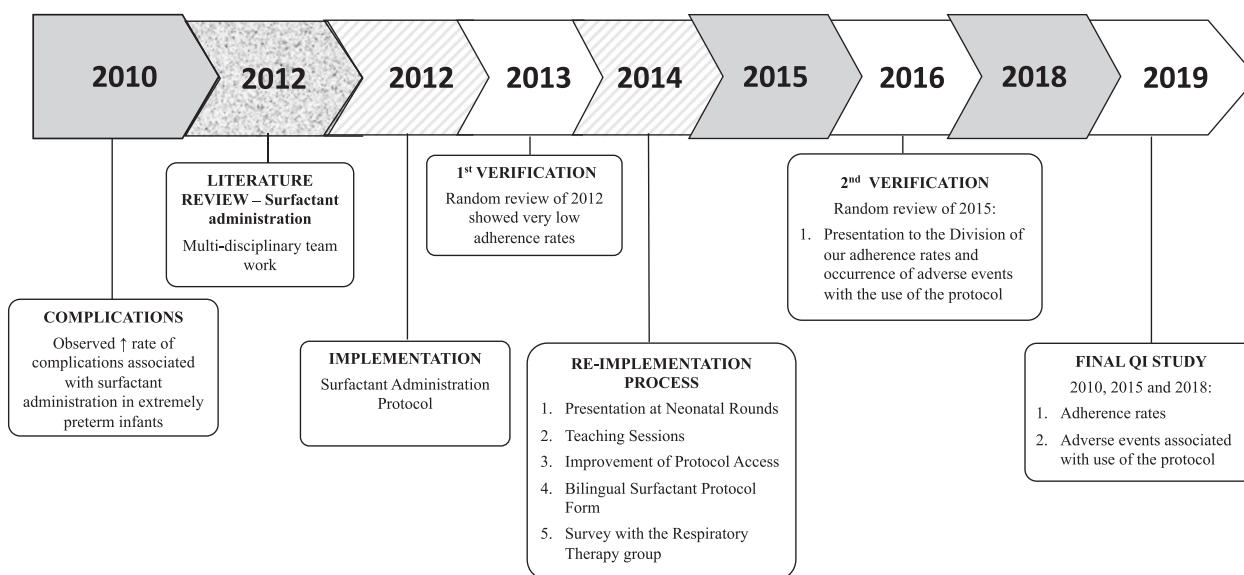


Fig. 1 Surfactant protocol implementation and re-implementation timeline. The interventions performed are described for each year. The final QI evaluation was done using the years of 2010, 2015 and 2018.

a few years ago we performed a review of the literature and identified three important aspects for optimal surfactant delivery into the pulmonary airways: use of large volumes by bolus administration, manual bagging, and recruitment of the lungs prior to instillation [12]. This led to the implementation of a bovine lipid extract surfactant administration protocol in our unit with the aim to streamline administration techniques and decrease rates of adverse events, notably SAOs. Thus, the primary objective of the quality improvement (QI) study is to evaluate the occurrence of severe airway obstruction events.

Methods

Context

The administration of the bovine lipid extract surfactant in extremely preterm infants has been reported as associated with adverse events such as SAOs. In 2010, we observed a rate of 26% of SAO in infants with birth weight (BW) < 1250 g that received surfactant. This finding combined with inconsistent surfactant administration techniques prompted the development of an evidence-based protocol for surfactant administration in our unit. The aim was to decrease SAO events from 26 to 2% over a 2-years period following protocol implementation. In this QI study we assessed all steps involved during the overall period of 8 years (2011–2019).

Population and site

Infants <32 weeks of gestational age (GA) treated with surfactant therapy at the Royal Victoria Hospital or

Montreal Children's Hospital during the study periods, were analyzed. Patients were identified using the local Canadian Neonatal Network databases. Infants with a genetic surfactant deficiency syndrome, complex genetic syndromes, or infants where surfactant was given at referring centers or during transport, were excluded.

Planning the interventions

The surfactant administration protocol was developed during the year of 2011 by a multidisciplinary committee based on the best-quality evidence available. (Fig. 1) Details of the protocol have been published [12] and are publicly available (<https://www.cjrt.ca/wp-content/uploads/surfactant-administration-in-neonates-a-review-of-delivery-methods.pdf>). Briefly, it includes surfactant administration criteria and guidance for all phases of drug delivery (before, during and after administration). Of note, a pre-recruitment maneuver using a positive end expiratory pressure of 8 cm H₂O for a minimum of 30 s should be performed without changing the tidal volume of 4–5 mL/kg used during the assisted control volume guaranteed mode of ventilation. Furthermore, surfactant is then given as bolus, divided into two equal aliquots, and while providing manual ventilation with the flow-inflating bag or a T-piece during drug instillation. Vital signs are recorded carefully by both the bedside nurse and the respiratory therapist and no suctioning of the endotracheal tube was to occur until 2 h post administration.

Planning the study of the interventions

In this QI study, in order to evaluate the impact of the surfactant administration protocol three epochs (*E*) were

established: E_0 = before surfactant protocol (January–December 2010); E_1 = after protocol development, implementation, and re-implementation (January–December 2015) and E_2 = 3–4 years after protocol re-implementation (January–December 2018).

Description of measures

The outcome measure of the study was the number of SAO events. Process measure was adherence to the protocol and balancing measures were the occurrence of adverse events associated with surfactant administration such as pneumothorax, pulmonary hypertension, and episodes of bradycardia and desaturations. All information was extracted from medical records but for E_1 and E_2 data was also obtained from a specially designed form filled by respiratory therapy during drug administration.

The following variables were also extracted: GA, BW, gender, singleton status, antenatal steroid therapy (complete or incomplete), mode of delivery, maternal use of antibiotics, Apgar scores at 1 and 5 min, positive pressure ventilation requirements and need for intubation at delivery.

Definitions

The lack of compliance to any of the three steps established in the protocol was defined as *non-adherence* and *unknown adherence* was defined as absence to fully fill the form. Minor events were defined as hypoxia (oxygen saturation <80%) and/or bradycardia (<100 bpm) and major events as pulmonary hypertension (pre/post SpO₂ difference greater than 5–10% checked in the surfactant form by the respiratory therapist or diagnosed by the medical team within 48 h after procedure), pulmonary hemorrhage, pneumothorax, and SAO. SAO was defined as an episode of hypoxia (<80% saturation)/bradycardia (<100 bpm) AND any of the following: (a) need to increase PIP, (b) need to suction the ETT, (c) lack of chest rise or (d) need for ETT exchange. Major complications were reported only if they occurred within a certain timeframe to ensure causality: (a) pulmonary hemorrhage and pulmonary hypertension within 48 h after the procedure; (b) pneumothorax within 24 h after the procedure and (c) SAOs during or immediately at the end of the procedure.

Statistical analysis

Categorical variables are expressed as counts and percentages and continuous variables as mean \pm standard deviation (SD). The *Chi-square test* and the *Fischer exact test* were used for categorical variables and the *Student t test* for continuous variables. All results were analyzed for infants that received surfactant with full protocol adherence during

the study period and for the overall population. Statistical analysis was performed using the software SPSS (Statistical Package for the Social Sciences). A p value <0.05 was considered as statistically significant.

Ethical considerations

The protocol development and implementation followed all steps of the McGill University Health Center policies and was approved for implementation and use in 2012. The present study was approved by the research ethics board of the institution.

Plan-Do-Study-Act 1 (January–December 2010)

A number of complications were reported by different neonatologist, respiratory therapists, and neonatal nurse practitioners during the administration of the bovine lipid extract surfactant in the delivery room or the neonatal intensive care unit. Cases were discussed in morbidity rounds and given lack of consistency in administration techniques used and a previous study from Canada describing similar events [10], general consensus was attained for the need to develop an evidence-based protocol for surfactant administration in our unit (Fig. 1).

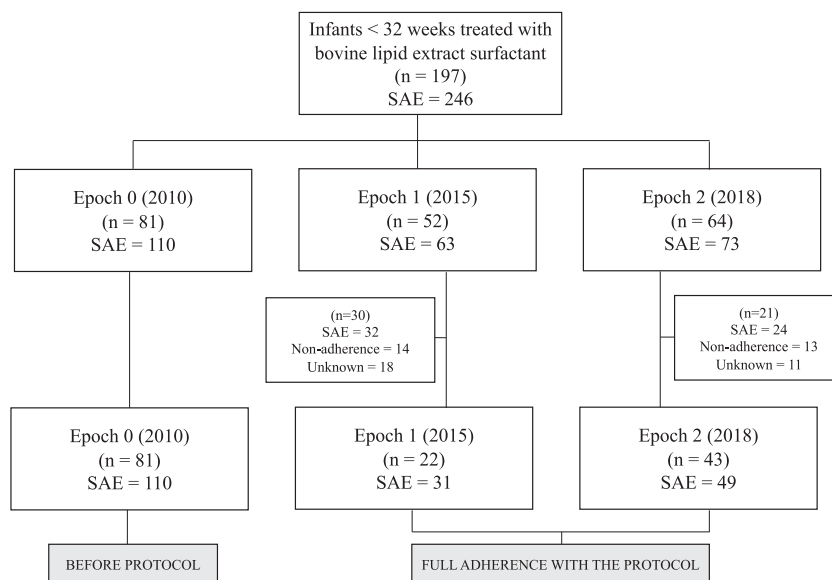
Plan-Do-Study-Act 2 (January 2011–December 2014)

The protocol was developed in 2011 and implemented in 2012. In 2013, a random review for the 2012 year revealed very low adherence rates. Thus, during the year of 2014 a re-implementation process was undertaken using several steps: presentation of the protocol at Neonatal Grand Rounds, teaching of the details and reasons for the three main steps to all respiratory therapists and neonatologists, improvement in protocol access at bedside and development of a *surfactant administration form* (bilingual) to be used during each administration. (Appendix 1) This form included a stepwise checklist to be filled by the respiratory therapists and a comprehensive description of the protocol on its back side. The form remained at bedside for 24 h after each surfactant administration event to ensure that information of any adverse complication was properly recorded. A carbon copy of the form was collected afterwards and kept with the respiratory therapy manager (ML); the original was left in the medical record. In addition, an internal survey with our respiratory therapy group was done to assure their knowledge on the protocol, specifically the three main steps.

Plan-Do-Study-Act 3 (January 2016–October 2019)

In 2016, a second audit on the use of our surfactant administration protocol was done for the year of 2015.

Fig. 2 Flow diagram of the population. SAE = surfactant administration events.



Adherence rates and conclusions were then presented along with results of the internal survey done in 2014 to highlight the areas that could be improved. No other implementation process took place after this point. Finally, in 2019 this QI study was designed to evaluate adherence to the protocol and rates of adverse events (Fig. 1).

Results

The initial steps of the intervention and their evolution over time are included in Fig. 1. During the three epochs selected a total 197 infants received 246 surfactant administration events (Fig. 2): $E_0 = 81$ infants (110 events), $E_1 = 52$ infants (63 events), and $E_2 = 64$ patients (73 events). In both E_1 and E_2 , infants were of significantly lower GA and BW, had lower Apgar scores at 1 and 5 min, and required more positive pressure ventilation despite improved usage of antenatal steroid therapy when compared to E_0 (Table 1).

Process measure—adherence to the protocol

Protocol adherence increased over time, from 49% (E_1) to 67% (E_2) (Appendix 2). The reasons for lack of adherence were: $E_1 = 14$ events did not follow the protocol and 18 unknown adherence and $E_2 = 13$ events did not follow protocol and 11 unknown adherences (Table 2).

Outcome and balancing measures—SAO and other adverse events associated with surfactant administration

Full adherence to the protocol. There was a significant decrease in SAO events in infants that received surfactant in

Table 1 Population demographics.

	E_0 (n = 81)	E_1 (n = 52)	E_2 (n = 64)
Gestational age (weeks)	29.8 ± 4.8	28.6 ± 3.5*	28.5 ± 4.1*
Birthweight (g)	1583 ± 956	1234 ± 648*	1297 ± 771*
Gestational age <32 weeks	52 (64)	42 (81)*	52 (81)*
Male	53 (65)	27 (52)	39 (61)
Singleton	65 (80)	44 (85)	47 (73)
Outborn	31 (38)	5 (10)*	9 (14)*
Antenatal steroids—complete	27 (33)	29 (56)*	34 (55)*
Antenatal steroids—none	32 (39.5)	8 (15)*	13 (20)*
Antibiotics (<24 h prior delivery)	43 (53)	36 (69)	40 (62.5)
Vaginal delivery	34 (42)	23 (44)	22 (34)
Cesarean delivery	47 (58)	29 (56)	42 (66)
Apgar 1 min	5.3 ± 2.7	3.8 ± 2.0*	3.92 ± 2.7*
Apgar 5 min	7.0 ± 2.2	5.7 ± 1.9*	5.79 ± 2.1*
Positive pressure ventilation	55 (68)	48 (94)*	61 (95)*
Intubation	41 (51)	28 (54)	30 (47)
Surfactant administration events	110	63	73

E = epoch year; $E_0 = 2010$, $E_1 = 2015$, and $E_2 = 2018$. Results are expressed as n (%) or mean ± SD.

* $p < 0.05$ for E_0 vs E_1 and E_0 vs E_2 .

full adherence with the protocol (Table 2 and Fig. 3). Indeed, during E_1 and E_2 a total of 80 administrations followed the protocol with only one SAO event (1.25%). Also, no episodes of hypoxia/bradycardia and pulmonary hypertension, and no additional side effects were detected. No case of pneumothorax occurred during E_0 and only two cases (2.5%) were noted during E_1 and E_2 .

Overall population. Following protocol implementation fewer (but not significant) minor events were observed during E_1 and E_2 . Importantly, a significant reduction in SAOs was noted: $E_0 = 29$ vs $E_1 = 2$ ($p < 0.005$) and $E_0 = 29$ vs $E_2 = 2$ ($p < 0.005$). Both SAO events in E_1 and one event during E_2 occurred in infants with unknown protocol

adherence. In fact, the incidence of SAOs with unknown full adherence was 14% (E_1) and 8% (E_2). Two cases of pneumothorax were noted during E_1 and E_2 when the protocol was not followed. The details of all adverse events for the overall population are described in Appendix 3.

Table 2 Adherence to the protocol and adverse events with full adherence.

	E_0 ($n = 110$)	E_1 ($n = 63$)	E_2 ($n = 73$)
Protocol adherence			
Full adherence (all 3 steps)	–	31 (49)	49 (67)
No-adherence	–	14 (22)	13 (18)
Unknown ^a	–	18 (29)	11 (15)
Adverse Events			
	($n = 110$)	($n = 31$)	($n = 49$)
Major			
Severe airway obstruction	29 (26)	–	1 (2)*
Pneumothorax	–	1(3)	1(2)
Pulmonary hemorrhage	2 (2)	1(3)	–
Pulmonary hypertension	1 (1)	–	–
Minor			
Hypoxia	8 (7)	4 (13)	4 (8)
Bradycardia	–	–	–
Hypoxia and Bradycardia	6 (5)	–	–

$E =$ epoch; $E_0 = 2010$, $E_1 = 2015$, and $E_2 = 2018$. Results are expressed as n (%); .

* $p < 0.005$ for E_0 vs E_1 and E_2 .

^aBlank spaces in the surfactant administration form were categorized as unknown adherence.

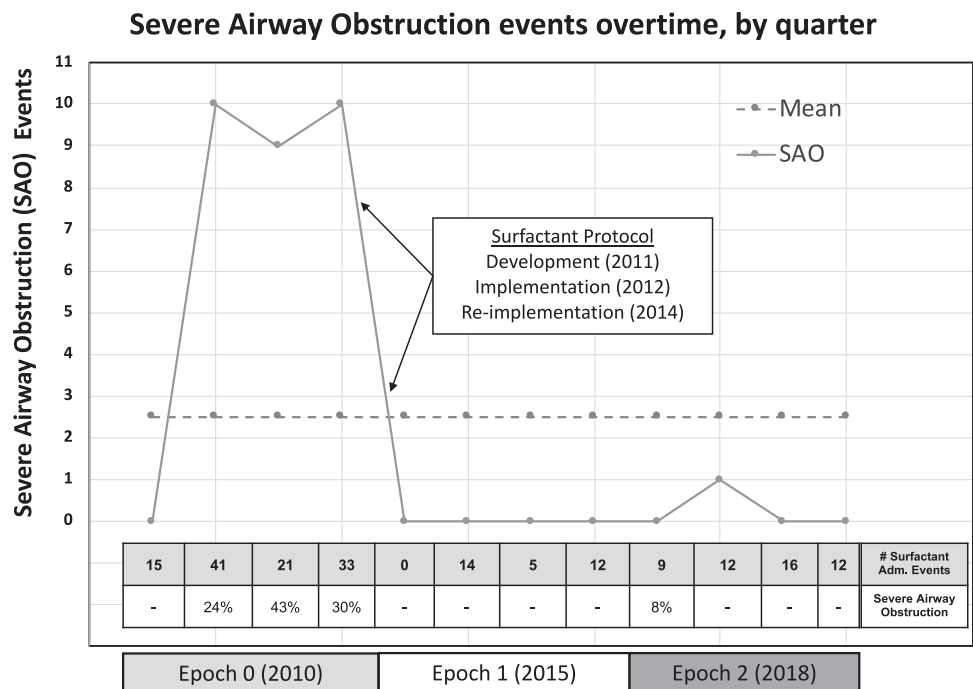
Discussion

In this study, adherence to a standardized surfactant administration protocol increased over time and was associated with a significant decrease on the number of SAO and hypoxia/bradycardia events, when using the bovine lipid extract surfactant for treatment of respiratory distress syndrome. Importantly, this improvement was sustained over time and occurred in a population of lower GA and BW.

Clinical protocols are important pathways used to implement evidence-based therapies and reduce unnecessary variations in practice [13, 14]. Indeed, protocols for respiratory care have been increasingly used by Canadian NICUs [15, 16]. However, compliance rates are generally reported as low (25–50%) which can be improved by using of a multidisciplinary approach as done in our center [14]. Unfortunately, our study lacks precision on protocol adherence calculation since incomplete forms were classified as unknown. Thus, adherence rates could have been higher than the 67% reported on E_2 . Nevertheless, it is important to highlight that higher adherence rates (>90%) are possible but require a massive effort by institutions in their initial phases of implementation [17].

Despite the bovine lipid extract surfactant being a low-cost preparation used for several years, only six clinical studies were performed: four randomized controlled trials (RCT) [9, 18–20], one prospective observational study [10] and one retrospective single center analysis [21]. Unfortunately, except for one study [10], details on the surfactant

Fig. 3 Severe airways obstruction events over time. SAO = Severe airway obstruction. Each point represents the number of SAO events for the periods of January–March, April–June, July–September and October–December; for all Epochs of the study. The box shows the number of surfactant administration events and percentage of SAO for each specific period. In Epochs 1 and 2 only surfactant administration events with full adherence to the protocol were included.



administration technique is not provided and reports on major adverse effects were quite variable. The only large multicenter trial (unpublished) compared the BLES[®] with colfosceril palmitate (Exosurf[®] Neonatal; Glaxo Wellcome). A total of 568 infants of significant higher GA and BW received BLES[®] and a 6% incidence of any type of ETT obstruction (not defined) was reported [9]. In 2005, Lam et al. compared BLES[®] with a bovine lung extract (Beractant[®], Ross Laboratories, Columbus, OH) and no adverse events were described with both preparations [18]. A recent small multicenter Canadian RCT compared BLES[®] with an extract of natural porcine lung surfactant (Curosurf[®], Chiesi Pharmaceuticals, Parma, Italy) [19]. Surfactant was administered by using one or two aliquots instilled as bolus and five episodes (11%) of SAO occurred only in infants who received BLES[®]. Unfortunately, details on the administration technique/protocol were not described [19]. In 2018, another RCT included 100 infants (median of 30 weeks of GA) and compared BLES[®] with a bovine lung extract (Beractant[®]). Again, no significant difference on complications was observed between the groups and no case of SAO was stated [20]. Altogether, these trials enrolled 692 infants and some type of ETT obstruction was reported in between 6 and 11% of infants treated with BLES[®] [19].

A retrospective single center study done in Canada investigated the time to reach room air following BLES[®] administration in infants <37 weeks and no side effects were identified [21]. In the only prospective study, we described an incidence of 15% of SAO, mostly in extremely low birthweight infants (83%), an incidence similar to the Canadian RCT [19]. In that study a non-evidence based surfactant administration protocol that included multiple aliquots, no disconnection from the ventilator, and no lung recruitment prior to instillation was used [10]. Thus, our administration protocol was modified to promote better lung distribution without adverse events while using the same surfactant preparation [12]. Surfactant was given after a quick lung recruitment maneuver (30 s) and by bolus into two aliquots, and manual bagging was done after instillation of each aliquot (Appendix 1). It is important to note that in the present study, the lung recruitment strategy prior to the first dose was not tested independent of the other interventions and the use of positive pressure prior to surfactant administration may be harm in infants who have not been exposed to antenatal steroids as previously demonstrated in animal studies. Interestingly, with this modified technique the number of SAO events significantly decreased on epochs E_1 and E_2 combined ($p < 0.005$). Indeed, only one SAO occurred in the 80 administrations performed in full adherence with the protocol. These rates of SAO are significantly lower than previously reported [10, 19], and demonstrate the critical role of surfactant delivery technique to these immature infants when using a preparation that

requires high instillation volumes [9]. Indeed, during the years of 2015 and 2018, a SAO rate of 14% (E_1) and 8% (E_2) was observed when adherence to the protocol was unknown; within the range reported by the literature. Full adherence to the protocol was also associated with a significant decrease in hypoxia/bradycardia events and no cases of pulmonary hypertension. Furthermore, when the protocol was fully followed only two cases of pneumothorax were detected (2.5%), a rate lower than that observed in large RCTs where surfactant was only administered to immature infants that failed an initial conservative approach of non-invasive support from birth [1–3], as the case for E_1 and E_2 .

The results of our study demonstrate that surfactant administration technique should consider the type of surfactant used and target population, as preparations using much lower administration volumes (2.5 mL/kg) are effective and do not report such adverse events without using all the steps outlined here [1]. This is probably due to the favorable tridimensional anatomy of the preterm lungs for adequate drug distribution even at lower instillation volumes [22]. Therefore, neonatal units should implement local evidence-based protocols for surfactant administration including costs analyzes while ensuring optimal care. In our case, the cost of the bovine lipid extract surfactant is estimated between two to four times less expensive (per patient/kg) than the other two available preparations in Canada (data from 2019 obtained from IQVIA Solutions Canada Inc. and our Pharmacy Department).

The study reviewed a single center experience making difficult to ascertain generalizability of the work. Some other limitations were the inability to assure correct fulfilling of the surfactant form and missing data due to its retrospective nature. Thus, we analyzed outcomes with full protocol adherence and for the overall population. The study reviewed more than 200 administration events in a high-risk preterm population receiving a type of commonly used surfactant. Moreover, we used a nationally well-organized database to capture all infants who received surfactant. In addition, by using the specifically designed forms for each surfactant administration, data related to complications was prospectively collected for several years allowing a more reliable analysis of adherence rates and adverse events. Indeed, this is the first study specifically investigating the impact of a standardized surfactant administration protocol on rates of adverse events when using a specific low-cost and effective surfactant.

Conclusion

Adherence to a bovine lipid extract surfactant evidence-based administration protocol improved over time and was

associated with a significant decrease in the number of severe airway obstruction and hypoxia/bradycardia events. Importantly, this improvement was sustained over years while using a low-cost surfactant preparation despite treating a smaller and more immature population. Better adherence rates may further improve outcomes. Importantly, results of our study demonstrate that surfactant administration technique is an important variable related to adverse events and should be tailored to the type of surfactant and population treated. Future studies in this area should clearly define and report the technique used during surfactant administration.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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